II. Interview Summary

Applicants' representative thanks the Examiner for the courtesies and attention shown during the interview held on 14 March 2008 with the undersigned and Dr. Ian Tomlinson, during which all pending claims were discussed.

The discussion involved prior art including *Dower, et al.*, and its focus on combining V_H and V_L to give rise to an antigen binding site.

Sastry, et al., and its use of lambda cloning vectors to clone heavy chain encoding nucleic acids was also discussed as was *Sastry's* discussion of V_L and V_H pairing and each chain's relative contribution to antigen binding.

Similarly, the focus of *Ladner, et al.*, on V_H V_L binding was discussed. Applicants' representative also discussed V_H binding and V_H binding specificity. No agreements were reached.

III. Patentability Arguments

1. The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

At page 4 of the office action, the Examiner rejected claims 9 and 13-17 under 35 U.S.C. § 102(e) as allegedly being anticipated by US patent 5,427,908 to *Dower et al (Dower)*. The applicants respectfully traverse the rejection and request reconsideration in view of the following.

The pending claims of the instant application require that the binding molecule "...consists of an antibody heavy chain variable domain... (see claim 9).

At page 4 of the office action, the Examiner alleges that *Dower* discloses phage display of V_H in column 3, lines 28-42. The passage referred to by the Examiner states:

> When the protein of interest is an antibody of a desired binding specificity, the antibody may be of any of the known isotypes or subclasses for a particular species, and may be a single-chain or two-chain binding complex or portion thereof. For instance, only the variable antigen-binding regions of heavy (V_H) and/or light (V_L) chains ***may be identified and cloned; the binding fragments (F_v) or Fab encoded thereby may find use either as a binding***

> ***fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions***. The characteristics of the constant region domains will depend to a large extent on the use intended for the antibody, e.g., diagnostic and/or therapeutic applications, catalytic antibodies, etc.

(Emphasis added.)

This passage does not state that the binding domain consists of an "...antibody heavy chain variable domain..." as required by the pending claims. The passage provides that ...V_H and/or V_L chains may be identified and cloned. It then states that,

> *...the binding fragments (F_v) or Fab encoded thereby may find use either as a binding fragment, joined to constant regions of heavy or light chains, or joined to other proteins having desired effector functions.*

F_V fragments consist of both a heavy chain variable region (V_H) and a light chain variable region (V_L) which together form an antigen binding site. Fab fragments consist of a V_L and a V_H, each of which comprise a constant region which when combined constitute an antigen binding fragment. The passage in *Dower* referred to by the Examiner does not state that a heavy chain variable domain is a binding molecule. It refers to the combination of V_H and V_L that gives rise to the F_V and/or Fab binding fragments.

The cloning of V_H and/or V_L domains and their combinations are further elaborated in *Dower*, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together V_H and V_L domain sequences in associated pairs to form binding domains. Thus, *Dower* discloses that its method is useful for identification and cloning of a new variable V_H domain and V_L domain which can be used to form F_V or Fab antigen binding fragments and does not disclose the display of a binding molecule consisting of a V_H domain on the surface of a filamentous phage.

This interpretation is further supported by the fact that the claims of *Dower* are directed to screening a DNA library for nucleotide sequences which encode,

> ...an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region... (See claim 1)

Further, Example 1 of *Dower* is similarly directed to display of Fab molecules, in which one polypeptide chain composed of V_H and C_H domains is presented as a fusion with bacteriophage

gene III protein and displayed with an associated second polypeptide composed of V_L and C_L domains to provide a binding domain formed by the combination of V_H and V_L chains and their associated constant regions together.

In summary, *Dower* relates primarily to display of Fab with a suggestion of Fvs, and not to the display on filamentous bacteriophage of binding molecules that consist of an antibody heavy chain variable domains as required by the present claims. Accordingly, Applicants respectfully submit that claims 9 and 13-17 are not properly anticipated by *Dower* and hereby request withdrawal of the rejections under U.S.C. §102(e).

2. The Rejections Under 35 U.S.C. §103 Should be Withdrawn

The Examiner has also rejected claims 9 and 13-17 under 35 U.S.C. §103(a) as allegedly unpatentable over a combination of WO 90/02809 ("*Ladner*") and Sastry et al. PNAS 86: 5728-5732 ("*Sastry*"). The Examiner characterized *Ladner* as disclosing the expression of scFv on the surface of filamentous phage. The Examiner admits that *Ladner* does not teach the expression of V_H. See ¶3 at page 7 of the office action.

The Examiner characterized *Sastry* as teaching "methods of displaying V_H utilizing lambda phage wherein the VH are obtained from lymphocytes." See ¶4 at page 7 of the office action, (emphasis added).

The Applicants respectfully traverse the rejections and submit that *Sastry* does not disclose a method in which a V_H domain is displayed on the surface of a filamentous bacteriophage. In fact, *Sastry* simply teaches the cloning of V_H regions from mouse spleen RNA using lambda phage cloning vectors with no display at all on the surface of any phage. On page 5728, right hand column, *Sastry, et al.*, in referring to problems of cloning V_H region states:

> "We report here solutions to this problem and present methodology for amplification and cloning of a diverse population of V_H regions from mouse spleen mRNA."

This is reiterated in *Sastry, at* page 5732, first complete paragraph, which states:

> We have used the PCR method for enriching V_H sequences. The method has been used to clone V_H sequences from hybridomas but not from spleen...

At page 7 of the office action, the Examiner states that "one having ordinary skill in the art would have been motivated to [combine *Ladner* with *Sastry*] because *Sastry* teaches that the heavy chains are responsible for the majority of antigen binding affinity of antibodies." More

specifically, the Examiner alleges that *Sastry* teaches that "the heavy chains are responsible for the majority of antigen binding affinity of antibodies" (see the introduction section at page 5728).

However, the referenced passage in *Sastry* only states that,

> "...it is apparent from x-ray crystallographic structures of antibodies, it is apparent that an appreciable amount of the binding energy comes from the heavy chain alone."

Applicants respectfully submit that "the heavy chain" does not equate to the V_H domain recited by the present claims. A heavy chain includes both the V_H and C_H domains of an antibody.

Further, a major part of *Sastry* focuses on, how,

> "...both heavy and light chains contribute to the formation of the combining site...Thus, the combination of the heavy chain with any light chain that allows formation of the combining site without creating unfavorable steric or electrostatic interactions should preserve a significant portion of the antibody specificity."

See Figure 1, (legend), page 5729.

Sastry, continues to emphasize the combination of V_H fragments with light chain (V_L) by stating at page 5728, right column, first paragraph:

> "...such that ultimately multiple V_H fragments in combination with a few light chains could be screened for binding and catalytic activity."

Further, in discussing the problems of producing functional antibodies, S*astry* states at

> Ultimately, the problem reduces to the extent to which the V_H binding energy can be complemented by light chains that were not selected during induction of an immune response (page 5752, left column).

In conclusion, *Sastry* only discloses cloning antibody heavy chain variable region specific cDNA's using lambda phage. *Sastry* does not disclose display of V_H domains capable of binding an antigen on a filamentous bacteriophage or any phage for that matter. *Sastry* does repeatedly provide that a heavy chain region should be paired with light chains to give rise to catalytic antibodies.

The Examiner also states that *Ladner* teaches the expression of scFv's on the surface of filamentous phage but admits that it does not teach display of V_H domains, concluding that the combination of display of scFvs allegedly suggested by *Ladner* with the V_H domains suggested by *Sastry* renders the present invention obvious. It should be noted that scFvs allegedly

suggested by *Ladner* contain a combination of V_H and V_L that must "fold together to bind antigen." See passage bridging pages 17 and 18 of *Ladner*. However, applicants submit that if *Ladner* is combined with *Sastry* as suggested by the Examiner then a person skilled in the relevant art is still left with a method that utilizes a combination of a light chain with a heavy chain is used because *Sastry* teaches that such combinations give rise an antigen binding site and because the scFv described by *Ladner* also contains a combination of V_H and V_L which must fold together to form an antigen binding site.

Accordingly, the combination of *Ladner* with *Sastry* does not teach or suggest the display of a binding molecule consisting of an antibody heavy chain variable domain on the surface of a filamentous bacteriophage, and therefore cannot properly render the pending claims obvious. In view thereof, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).